PCT/EP2003/008312

Translation

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 15765/PCT ge | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/EP2003/008312 | International filing date (*day/month/year*) 28 July 2003 (28.07.2003) | Priority date (*day/month/year*) 29 July 2002 (29.07.2002) |
| International Patent Classification (IPC) or national classification and IPC G01N 15/12 | | |
| Applicant EVOTEC OAI AG | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 26 January 2004 (26.01.2004) | 09 November 2004 (09.11.2004) |
| Name and mailing address of the IPEA/EP<br><br>Facsimile No. | Authorized officer<br><br>Telephone No. |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/008312

## I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-22, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-28, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages 1/4-4/4, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP 03/08312

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-28 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 5, 16, 23, 24 | YES |
| | Claims | 1-4, 6-15, 17-22, 25-28 | NO |
| Industrial applicability (IA) | Claims | 1-28 | YES |
| | Claims | | NO |

2. Citations and explanations

Reference is made to the following documents:

D1: US-A-4 420 720 (NEWTON WILLIAM A ET AL) 13 December 1983 (1983-12-13)

D2: DE-A-22 01 894 (LICENTIA GMBH) 19 July 1973 (1973-07-19)

D3: WO-A-00/37628 (FUHR GUENTER; GRADL GABRIELE (DE); MUELLER TORSTEN (DE); SCHNELLE) 29 June 2000 (2000-06-29)

D4: FIEDLER STEFAN ET AL: "Dielectrophoretic Sorting of Particles and Cells in a Microsystem" ANALYTICAL CHEMISTRY, Vol. 70, No. 9, 1 May 1998 (1998-05-01) pages 1909-1915, XP000755524, ISSN: 0003-2700

D5: GAWAD S et al: "Micromachined impedance spectroscopy flow cytometer for cell analysis and particle sizing" LAB ON A CHIP, ROYAL SOCIETY OF CHEMISTRY, CAMBRIDGE, GB, Vol. 1, 13 August 2001 (2001-08-13), pages 76-82, XP008028057, ISSN 1473-0197.

1. Documents D4 and D5 are introduced herewith into the proceedings. Document D4 describes a method for the dielectrophoretic focusing and sorting of particles and cells in a microfluidic system, in which analysis of the particles is carried out with the aid of a microscope or an epifluorescence detector comprising

a camera and video system. Document D5 also describes a microfluidic system in the form of a flow cytometer which is used for measuring the impedance of particles and cells; in addition to hydrodynamic focusing, D5 also mentions a system for the dielectrophoretic manipulation of cells for the positioning, aligning and sorting of cells. Document D4 is now considered to be the closest prior art for the application.

2. The present application does not comply with the requirements of PCT Article 33(1), because the subject matter of independent claims 1 and 14 does not involve an inventive step within the meaning of PCT Article 33(3).

2.1 Document D4 discloses the following technical features of claim 1 (the references in parentheses are to D4), namely:

method for measuring in a microfluidic microsystem which comprises a compartment which is traversed by a flow of a liquid containing at least one [sic!] suspended particle (abstract and page 1911, second column, last paragraph; page 1913, second column, lines 5 to 8; page 1915, second column, fourth paragraph and figure 2),

focusing of the at least one [sic!] particle [sic!] being carried out at a predefined distance relative to the detector (page 1911, second column, last paragraph to page 1913, second column, line 7; figures 2 to 4),

characterized in that
the focusing comprises a movement of the at least one [sic!] particle [sic!], relative to the liquid flowing in the compartment, as a result of dielectrophoretic forces which are exerted by at

least two focusing electrodes (page 1912, first column, line 4 to page 1914, second column, line 2).

The at least two focusing electrodes are the electrode pairs of the planar funnel and the aligner.

2.2 Claim 1 contains the following features in addition to those of D4:

(1) the measurement method is a method for measuring impedance;

(2) the detector is an impedance detector; and

(3) at least one impedance detector is arranged in the compartment and records at least one impedance value for the detection of the at least one [sic!] particle [sic!], which impedance value is characteristic of the impedance of the compartment and varies in a predetermined manner in the presence of the at least one [sic!] particle [sic!].

2.3 The technical problem which is solved by features (1) to (3) in item 2.2 of this report is the counting of the particles according to the Coulter principle. Features (1) to (3) are features of a Coulter particle counter which are known *per se* in the prior art.

2.4 Document D4 discloses, on page 1915, second column, fourth paragraph, the integration of the dielectrophoretic elements described in D4 in particle counting devices and flow cytometers. Since a person skilled in the art knows that a conventional embodiment of a particle counter is an impedance-measuring device based on the Coulter principle, he would naturally follow the suggestion of the authors of D4 and integrate the dielectrophoretic focusing

device known from D4 into a microfluidic Coulter particle counting device known from the prior art, which could be, for example, the device known from D5 (D5: page 76, first column, third paragraph to page 77, first column, first paragraph, figures 1 and 2; page 79, second column, second paragraph and figure 5), without the need for an inventive step: he would only need to replace the optical microscope or epifluorescence microscope explicitly known from D4 for observing and evaluating the particles (see page 1911, second column, sixth paragraph and page 1913, second column, lines 5 to 7) with a prior art impedance detector (see, for example, D5 (but also D1 or D2)). In addition, D5 explicitly refers to the importance of precise particle focusing (page 79, second column, last sentence of the second paragraph).

Consequently, claim 1 does not comply with the requirements of PCT Article 33(1) and (3).

3. Claim 14, which relates to a measurement device for impedance measurement, discloses, in addition to the technical features of claim 1, that the focusing device forms a "funnel-shaped field barrier" in the compartment. This feature is evidently known for the same technical purpose, namely focusing, from D4 (see page 1912, first column, lines 10 to 13) ("planar funnel", page 1912, first column, second paragraph) and therefore claim 14 obviously also fails to comply with the requirements of PCT Article 33(1) and (3) for inventive step.

4. The additional technical features of dependent claims 2-4, 6-13, 15, 17-22 and 25-28, which go beyond those of the claims to which they refer, are known for the same or similar technical purposes from the prior art, according, in particular, to documents D1 to D5,

and therefore do not comply with the requirements of PCT Article 33(1) and (3) for inventive step.

D1 to D3 disclose the following features:

D1: a particle analyser based on the Coulter principle for counting, measuring and analysing particles;

D2: a method for counting and characterizing particles; and

D3: a microsystem for cell permeation and cell fusion with the aid of dielectrophoretic forces. Although D3 does not disclose impedance measurement, the document is cited here because of the dielectrophoretic focusing of particles in "the range of interest" (see page 12, third paragraph to page 13, lines 1 to 4; page 14, second paragraph and figure 2 of D3, in respect of dependent claims 21 and 22).

5. The additional technical features of claims 5, 16, 23 and 24, which go beyond those of the claims to which they refer, appear, at the present stage of the proceedings, to comply with the requirements of PCT Article 33(1) to (3).